INSTRUCTOR'S GUIDE

REGULATORY PATHWAYS FOR PEDIATRIC MEDICAL DEVICES: MARKETING A PEDIATRIC MEDICAL DEVICE VIA A HUMANITARIAN DEVICE EXEMPTION

INTRODUCTION

This case study uses a fictitious medical device called the Pediatric Hope, LLC. (PHL) System to illustrate the U.S. Food and Drug Administration's (FDA) expectations and considerations for the submission of a pediatric medical device. The case study also explains Humanitarian Use Device (HUD) designation and Humanitarian Device Exemption (HDE) approval requirements. An HDE is a regulatory process by which the FDA's Center for Devices and Radiological Health (CDRH) approves a medical device intended for use in patients with rare diseases or conditions. The purpose of this case study is to teach students about the HDE process (not the product or its technical aspects) using an example of a medical device for pediatrics. Therefore, minimum technical details of the PHL System are provided. Instructors can use the case study and the references as a spring board to focus on a regulatory topic (e.g., design validation, biocompatibility, clinical trials), a coordinated course (e.g., design controls for a medical device), or a more advanced regulatory science curriculum.

LEARNING OBJECTIVES

1. To examine the challenges and opportunities for marketing pediatric medical devices
2. To understand Premarket Assessment of pediatric device applications
3. To explore regulatory pathways for pediatric medical devices

TOPICS

Regulatory background of pediatric devices; regulatory pathways for pediatric devices; clinical study issues

ASSUMPTIONS

The case study is based on the following assumptions:

- Target audience is undergraduate/graduate students who have no experience in medical device development.
- Users of the case study are instructors who have some basic knowledge about FDA.
- Instructors may spend at least two instruction sessions to teach the materials, including student presentations.

Instructors should—

- Be familiar with the reference materials listed.
- Dedicate sufficient preparation time for class lecture.
- Instruct students to be prepared at least 2 weeks before class.
- Prepare, engage, and immerse students in the lessons learned from the case study.

SUGGESTED APPROACH

1. Preparing Students (Before Class): Students are required to review all the appendices and the background of the case, complete all readings and assignments, and be prepared before each class session.
2. Engaging Students (In Class): This session is a lecture on medical device regulatory pathways and uses a pediatric medical device as an example. It may take two sessions for instruction and student participation.
3. Immersing students (After Class): This is a team project for which students will work together to plan the submission of a pediatric device application.

STUDENT ACTIVITIES

SESSION 1

I. Review the following materials before Session 1:

1. Videos
   a. NIH Children and Clinical Studies

      (Approximately 10 minutes)

      http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php

   b. Children's Cardiomyopathy Foundation

      (Approximately 7 minutes)

      http://www.youtube.com/watch?v=yrBzgpoij30

   c. Cardiovascular System

      (Approximately 1 minute)

      http://www.nlm.nih.gov/medlineplus/ency/anatomyvideos/000023.htm

   d. FDA Patient Safety News Video—FDA-SHOW4-SEG1-Home Monitoring System for Pacemaker

      (Approximately 1 minute)

      http://www.accessdata.fda.gov/cdrh_docs/psn/video/mpeg/FDA-SHOW4-SEG1.MPG

   e. FDA Safety News Video—FDA-SHOW2-SEG3-Pacemaker for Treating Congestive Heart Failure

      (Approximately 1 minute)

      http://www.accessdata.fda.gov/cdrh_docs/psn/video/mpeg/FDA-SHOW2-SEG3.MPG

   f. Cardiac Conduction System

      (Approximately 1 minute)

      http://www.nlm.nih.gov/medlineplus/ency/anatomyvideos/000021.htm

   g. Arrhythmias

      (Approximately 1 minute)

      http://www.nlm.nih.gov/medlineplus/ency/anatomyvideos/000005.htm

2. Mandatory Reading

Note: A Draft Guidance is subject to change and is not for implementation.

   a. Premarket Assessment of Pediatric Medical Devices

      http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf

b. Humanitarian Device Exemption (HDE): Questions and Answers—Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm389154.htm

c. Humanitarian Use Device (HUD) Designations

http://www.fda.gov/downloads/ForIndustry/DevelopingProductsForRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/LegislationRelatingtoHUDsHDEs/UCM336515.pdf

3. Optional Reading

Note: A Draft Guidance is subject to change and is not for implementation.

a. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigation

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf

b. Guidance on IDE Policies and Procedures

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf

c. Information on Premarket Approval (PMA)

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm

II. Answer the following questions before Session 1—Fundamental Concepts:

1. Describe the indications for use of the PHL System.

The PHL System is intended to provide pacing therapies and cardiac assistance for pediatric patients 6 to 18 years of age who have restrictive cardiomyopathy. It is intended to provide pacing therapy and circulatory support as a bridge to pediatric candidates for cardiac transplantation.

Caution: Avoid getting bogged down with the technical details of the PHL System, as this could get complicated and distract from the point of the case, which is instruction about regulatory approval pathways. We suggest instructors avoid these technical details and focus instead on illustrating the elements of indications for use.

2. Justify why the HDE application is the appropriate regulatory pathway for the PHL System.

http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/default.htm

The intended use of the PHL System is to treat pediatric patients of restrictive cardiomyopathy. According to the American Heart Association, the incidence of pediatric patients with this condition in 2009 was estimated between 300~1,750.

As defined in 21 CFR Part 814.3(n), a HUD is a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year."

Therefore, the PHL System is qualified to be designated as a HUD and an HDE can be submitted for marketing approval only because it meets the orphan subset threshold. That means that device can only be used for the subset of patients with the identified disease and use of the device in the remaining patients would be inappropriate because of some intrinsic feature of the device.

III. Additional References

1. The Federal Food Drug & Cosmetic (FD&C) Act

   http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugand Cosmetic ActFDCAct/default.htm

2. Sub Chapter II—Definitions § 321. Definitions [p. 32, paragraph(h)]

   http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapII-sec321.pdf

SESSION 2

I. Review the following materials before Session 2:

1. CDRH Learn Videos
   a. Overview of Medical Device Regulations

      (Approximately 31 minutes)

      http://fda.yorkcast.com/webcast/Viewer/?peid=040308365ec8405bad39b06de8561bdc1d

   b. Good Clinical Practice 101: An Introduction

      (Approximately 29 minutes)

      http://fda.yorkcast.com/webcast/Viewer/?peid=477af877491747379c36c4ab1c7421b9

   c. The Sponsor: Responsibilities in Medical Device Clinical Trials

      (Approximately 17 minutes)

      http://fda.yorkcast.com/webcast/Viewer/?peid=88f92205e9624bbea1d627126af5360f

   d. The Clinical Investigator: Responsibilities in Medical Device Trials

      (Approximately 14 minutes)

      http://fda.yorkcast.com/webcast/Viewer/?peid=29b55c1dd3f64d8fa74ca2227df14b39

2. Mandatory Reading
   a. ICH E6 Good Clinical Practice: Consolidated Guidance

      http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf

3. Optional Review and Readings
   a. 21 CFR 820: Quality System Regulation (CGMP) Video (up to slide 48 of 86)

      (Approximately 2 hours)

      http://fda.yorkcast.com/webcast/Viewer/?peid=dd2d4823b14a4e4ca6d60eae43c5ac9c

   b. Quality System Information for Certain Premarket Application Reviews

      http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf

   c. Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (p. 1-39)

      http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071986.pdf

II. Questions for in-class discussion:

1. What have you learned from the case study about the requirements of an HDE application?
   a. Prerequisites

HDE is an authorization to market a HUD (Humanitarian Use Device). Therefore, a medical device must obtain designation as a HUD before the submission of an HDE application. The sponsor must provide documentation, with appended references, to demonstrate that the device meets the definition of a HUD, outlined in 21 CFR Part 814.3(n): "a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year." The sponsor should submit the request for a HUD designation to the Office of Orphan Product Development (OOPD) before submitting an application for an HDE.

The HUD application should include the following information:

- A statement that the applicant requests HUD designation for a rare disease or condition or a specifically identified orphan subset of a non-rare disease or condition.
- The title, name, address, and telephone number of the applicant and the primary contact person(s). An e-mail address for the primary contact person(s) is recommended.
- A description of the rare disease or condition that the device treats or diagnoses, ideally with particular emphasis on the specific aspects of the disease or condition relevant to the functionality of the device, as well as the proposed indication(s) for use of the device and the reasons why such therapy is needed.
- A description of the device and a discussion of the scientific rationale for the use of the device for the rare disease or condition.
- Documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a rare disease or condition that affects or is manifested in fewer than 4,000 people in the United States per year.
- If the device is intended for diagnostic purposes, the population documentation must demonstrate that fewer than 4,000 patients per year would be subjected to diagnosis by the device for the disease or condition in the United States. [See 21 CFR Part 814.102(a)(5)]

Although a HUD designation from OOPD is a prerequisite for submitting an HDE marketing application to CDRH or the Center for Biologics Evaluation and Research (CBER), it does not by itself guarantee approval of the HDE application. For further information on HUDs, see the FDA guidance on Humanitarian Use Device (HUD) Designations.

The subsequent HDE application must include the following:

- An explanation of why the HUD would not be available unless an HDE were granted
- A statement that no comparable device (other than another HDE-approved HUD or a device under an approved IDE) is available to treat or diagnose the disease or condition
- A discussion of the risks and benefits of currently available devices or alternative forms of treatment in the United States

- An explanation of why the probable benefit to health from use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment
- The amount to be charged for the device

For further information on HDEs see the FDA guidance on Humanitarian Device Exemptions (HDE): Questions and Answers.

b. Justification for an HDE submission

The sponsor should ensure the following:

- No comparable device is available to treat or diagnose the same disease or condition
- A comparable device is available under another approved HDE application
- A comparable device is being studied under an approved Investigational Device Exemption (IDE) [21 CFR Part 814.104(b)(2)]

Furthermore, the sponsor needs to provide evidence to demonstrate the safety and probable benefits of the HUD. HDEs are exempt from the effectiveness requirements.

Probable benefit refers to sufficient evidence that the use of the device will provide benefits to health that outweigh the risk of injury or illness from the device's use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

c. Data extrapolation

Instructors are encouraged to discuss Appendix C of the case study in detail and reference this Web link: http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm285898.htm

2. Discuss the types of nonclinical testing or studies that should be addressed for the PHL System.

Instructors are encouraged to discuss Exhibit 2 in the case study to the extent appropriate that is relevant to a given class curriculum. For example, an engineering curriculum may focus more on reliability engineering aspects, while a science curriculum may emphasize the areas of biocompatibility and sterilization.

a. Nonclinical in vitro tests

Instructors may consider the electromechanical functional, reliability, durability, and shelf-life testing on the component, sub-system, and system level testing on each one of the three PHL Sub-systems:

1. Implantable Miniature Pump (IMP)
   - ✓ Stress/strain analysis on mechanical parts
   - ✓ Functional characteristics of the pump, e.g., pump speed, flow rate
   - ✓ Reliability of fail-safe features
   - ✓ Time to perform as intended without any failure
   - ✓ Environmental Stress Screening on components/sub-system
   - ✓ Sub-system Life Testing
   - ✓ Flow through the pump
   - ✓ Hemodynamic characteristics of the pump
2. Rhythm Pacing Controller (RPC)
   - ✓ Worst Case Circuit Analysis
   - ✓ Out of Sequence/Timing Analysis
   - ✓ Software Verification/Validation
   - ✓ Environmental Stress Screening on components/sub-system

❸ Energy Distribution Pack (EDP)
- ✓ Battery life (during use)
- ✓ Shelf life (Storage)
- ✓ Environmental stress on EDP
- ✓ End of Life Indication/Caution Mechanism

b. Preclinical in vivo tests

Preclinical studies (in vivo tests) involving animal testing on the PHL System will give a preliminary understanding of the device's risks. These studies provide information on the local and systemic responses to the device that go beyond what the sponsor can achieve from an in vitro study, and will help justify further human studies.

One of the first steps is to choose appropriate animal models to test the PHL System. There may not be a single animal model that can be used to support all preclinical tests. The sponsor may need to consult with the FDA if there is no scientifically-valid animal model for certain preclinical tests and/or to confirm the model they plan to use. The animal model the sponsor selects should provide a test system that offers the best attempt at simulating conditions in the human body.

Animal models for pediatrics may be juvenile animals, and the age, size, and developmental stage of a particular model may need to be selected to match the age or stage of development of a patient. The data collected from these animal studies will be used to demonstrate that the system is sufficiently safe to be used for human experiments. In collecting the data, the sponsor will need to follow Good Laboratory Practices (GLP).

3. What have you learned from the case study about the following aspects of Good Clinical Practices (GCP)?

a. Human subject protection

In pediatric research, children require special attention because of their vulnerabilities and developmental issues. Those involved in pediatric research must respect the autonomy and the individuality of children, be aware of children's apprehension about medical procedures, and acknowledge the fundamental biological differences between adults and children. Therefore, pediatric trials differ from adult trials. Practical and ethical issues on human subject protection must be addressed.

Some Examples of Biocompatibility Tests

Effects of Patient-contacting Materials	Test Purpose
Cytotoxicity	Evaluations involve the assessment and measurement of cell damage and measurements of cell growth and certain cellular metabolism.
Acute Systemic Toxicity	Typically, a rodent species (rat, mouse) will be used to evaluate adverse effects occurring at any time after single, multiple, or continuous exposures of a test sample within 24 hours.
Genotoxicity	Test using mammalian or non-mammalian cells, bacteria, yeasts, or fungi to determine whether gene mutations, changes in chromosome structure, or other DNA or gene changes are caused by the test samples. These tests can include whole animals.

4. Explain the roles and responsibilities of those involved in clinical investigations.

The roles and responsibilities of the clinical investigator, sponsor, and the institutional review board (IRB) are crucial in protecting the rights and welfare of the pediatric subject (see Table 4). Moreover, pediatric trials should be performed in institutions that provide a child-friendly atmosphere with a well-defined pediatric infrastructure and supportive personnel.

III. Additional References

1. FDA Good Laboratory Practices

   http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133765.pdf

2. 21 CFR Part 58—Good Laboratory Practices

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1

3. 21 CFR Part 820 Preamble—Quality System Regulation

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1

SESSION 3: STUDENT PROJECT AND PRESENTATION

I. Review the following materials before beginning the project:

1. HDE Approval Information of a Pediatric Ventricular Assist Device (VAD) – H100004

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H100004

2. HDE Approval Information of a Child Left Ventricular Assist System – H030003

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H030003

3. PMA Approval Information of a Ventricular Assist Device – P060040

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P060040

II. Answer the following questions for the team project:

1. Explain the challenges of marketing pediatric medical devices. Suggest ways to overcome these challenges.

There are at least three major challenges to marketing a pediatric medical device.

❶ Regulatory issues

- ✓ FDA guidance is helpful. Sponsors are encouraged to meet with the FDA throughout the device development process to receive feedback on their proposed studies. The HDE process has been revised and new rules have been published relating to the submission of information on pediatric device approval. (21 CFR Part 814)

❷ Clinical issues

- ✓ Eligible pediatric populations for clinical trials are small and clinically varied. Randomized controlled trials are difficult for recruitment. A potentially helpful development has been the acceptance of using the Bayesian approach for clinical studies. Sponsors are allowed to use valid statistical models for borrowing data from adult or other pediatric studies. Again, it would behoove a sponsor to discuss their plans to utilize alternative study designs with the appropriate review division at FDA before launching forth into their studies.

3. Economic issues
   - ✓ Development costs for pediatric devices are prohibitive. However, the enactment of the Pediatric Medical Device Safety and Improvement Act of 2007 (PMDSIA) and the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 has allowed HUDs to be sold for profit if they meet certain criteria as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN) determined by the FDA.

A HUD is only eligible to be sold for profit after receiving HDE approval if the device meets the following criteria (for purposes of this guidance, "eligibility criteria"):

1. The device is intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs; or
2. The device is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.

The ADN is determined by the FDA when approving the HDE. The ADN is defined as the number of devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States. When determining the ADN, FDA considers the number of devices per year reasonably needed to treat, diagnose, or cure an individual ("first multiplier") and multiplies that value by 4,000 ("second multiplier").

By law, the second multiplier is always 4,000, regardless of whether the target population estimate is fewer than 4,000 individuals. Therefore, the ADN will be equal to or greater than 4,000, depending on the value of the first multiplier.

See section 520(m)(6)(A)(ii) of the FD&C Act and section 613(b) of FDASIA for more details.

2. What are the ethical concerns of pediatric clinical trials?

The need to obtain knowledge about the effects of medical products in pediatric patients has to be balanced against the ethical concerns of protecting the individual child in clinical studies and respecting his/her integrity and personal dignity.

As research subjects, children have special needs because of their vulnerabilities and developmental needs. Those involved in pediatric research must respect the general principles of medical ethics:

- Respect for life, human dignity, and personal autonomy
- Beneficence (do some good)
- Non-maleficence (do no harm)
- Justice (receive deserved benefits)

(See ISO 14155:2011 or ICH E6 Good Clinical Practice)

3. Would you use data from other studies in the PHL System HDE application? Justify your decision. (Refer to Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials, p.17-19)

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf

The HDE: H030003 Summary of Safety and Probable Benefit posted on FDA's HDE Web site is a device of a different indication. However, its summary of clinical studies may not be suitable for PHL System use.

4. What are the scientific and regulatory challenges both the FDA and industry must consider when using data to extrapolate or establish probable benefit for the pediatric population?

   http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM285293.pdf

The following is a list of potential challenges in establishing probable benefit for the pediatric population:

- Pediatric trials have small sample sizes. This stems from the facts that diseases can have a low incidence and informed consent might be more difficult to obtain.
- Suitable control groups are lacking as parents or guardians are reluctant to allow their children to become test subjects and placebo might not be ethical.
- Trial times and costs may be increased due to the above challenges.
- Reference samples may be too voluminous to be obtained from neonates or small children.

Challenges in extrapolation mainly depend on the data exchangeability between adult and pediatric trials. Extrapolation may be made from adults to pediatric patients or between pediatric subpopulations if the course of the disease or condition, or the effects of the device on the two populations (between adult and pediatric or among pediatric sub-populations), are similar.

5. Describe how you would carry out the clinical investigations of PHL System. Explain the ways that you would protect the subjects of your studies.

   a. Refer to ICH E6 Good Clinical Practice: Consolidated Guidance (p. 1-38)

      http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf

   b. ICH E11 Clinical Investigation of Medicinal Products in the Pediatric Population (p.12-14)

      http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073143.pdf

The following is a list of suggested steps for conducting a clinical study on the PHL System:

Identify sponsor: Clinical studies are sponsored or funded by PHL. PHL is responsible for the study.

Establish protocol: Clinical study is conducted according to a plan known as a protocol. PHL should carefully design a study protocol to safeguard the participants' health and answer specific study questions. The protocol describes the following:

- Who is eligible to participate in the study (patient population)
- Details about tests and procedures
- The length of the study and what information will be gathered
- Appropriate endpoints, including safety endpoints and stopping criteria
- Adverse event reporting

- A clinical study is led by a principal investigator (PI), who is often a doctor. Members of the study team regularly monitor the participants' health to determine the study's safety and effectiveness. PHL will select a PI for the study.

Review protocol: An Investigational Device Exemption (IDE) allows an investigational device to be in a clinical study in order to collect safety and effectiveness data. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated. Each clinical protocol must also be approved and monitored by an Institutional Review Board (IRB) to ensure that the risks are minimal and are balanced by the device's potential benefits. An IRB is an independent committee that consists of physicians, statisticians, and members of the community who ensure that clinical studies are ethical and that the rights of participants are protected.

Establish informed consent to protect the participating subjects: Informed consent is the process of providing potential participants with the key facts about a clinical study before they decide whether to participate. The process of informed consent (providing additional information) continues throughout the study. In order to help a patient decide whether or not to participate, members of the study team explain the details of the study. Translation or interpretive assistance can be provided for participants with limited English proficiency. The study team provides an informed consent document that includes details about the study (i.e., its purpose, duration, required procedures, and who to contact for further information).

The informed consent document also explains risks and potential benefits. The participant then decides whether to sign the document. Informed consent is not a contract, as study volunteers are free to withdraw from a study completely or to refuse particular treatments or tests at any time. Doing so, however, will sometimes make them ineligible to continue the study.

6. Prepare an outline detailing an HDE submission for the PHL System.

   Refer to Case Study Exhibit 2 and Table 4, and the HDE Checklist

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions HumanitarianDeviceExemption/ucm056830.pdf

The Instructor may choose a publicly available HDE example to demonstrate the requirements for this project. Examples are available at the FDA Listing of CDRH Humanitarian Device Exemptions Web site. (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm)

Instructors may also refer students to use the HDE Ref. H030003 device as a guide for the completion of the project. (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H030003)

Students may use Exhibit 2 and Table 4 as a template to outline some details of the PHL System.

The HDE Checklist may also provide further information that FDA reviewers expect sponsor to provide.

1. FDA's HUD designation letter
    a. Rationale for therapy
    b. Describe the disease state of restrictive cardiomyopathy
    c. Explain why pacing and external blood pump are needed
    d. Expound on the science of the PHL System that treats restrictive cardiomyopathy
2. Justification for HUD with documentation
    a. Describe the challenges of the pediatric population with restrictive cardiomyopathy.
    b. Demonstrate that the PHL System treats patients that meet the definition of 21 CFR Part 814.3(n), i.e., show data to support that there are fewer than 4,000 U.S. pediatric restrictive cardiomyopathy patients and why the device is designed to only treat the population of pediatric restrictive cardiomyopathy—meaning it is for an orphan subset.
    c Cite supporting literature, research reports, etc
3 A statement indicating that the device is a Humanitarian Use Device (the HDE device label must include the following statement: "Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been demonstrated.")
4. Indication for use
5. Device description
6. Evidence (data) demonstrating device safety
    a. Preclinical studies (students may use their discussion results from Class Session 2 to answer the following):
        i. Bench tests (in vitro)
            - Component, sub-system, and system
            - Reliability and shelf-life
            - Biocompatibility and sterilization
        ii. Animal tests (in vivo)
    b. Clinical studies. Students may use their discussion results from Class Session 2 to answer the following:
        i. Study design considerations
            - Therapeutic objectives
            - Targeted patient population
            - Clinical protocol
        ii. Study results with summary of safety and probable benefits

        Instructors may provide guidance to students using HDE H030003 as an example. A general framework may include discussions on how PHL System performance meets predetermined expectations, for example, pacing and pump performance. Other areas may include a detailed record of anticipated versus actual adverse events before, during, and after clinical studies. A comparison of adverse events of marketed devices, adult or pediatric devices, may also be helpful. Instructors may also refer to HDE# H100004 for an additional class discussion.

7. A rationale supporting the probable benefit of the device

   HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Both clinical and nonclinical testing results can be scientific evidence in supporting benefit-risk determination.

   Instructors may explore the FDA Guidance, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf

   Instructors may use a couple of examples to demonstrate how probable benefit can be determined.

III. Additional References

Note: A Draft Guidance is subject to change and is not for implementation.

1. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigation

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf

2. Information on Premarket Approval (PMA)

   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm

3. HUD Designations Guidance

   http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm336515.pdf

4. Humanitarian Device Exemption (HDE): Questions and Answers – Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff

   http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm389154.htm

5. Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff Guidance

   http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf